Review

Pilomotor Seizures: An Update on This Rare Semiology Manifestation and its Etiology

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Abstract
Ictal piloerection is a rare seizure manifestation and usually reported with temporal lobe epilepsy. There was no specific etiology associated with pilomotor seizures which were described in a wide variety of lesional as well as nonlesional epilepsies. This paper will review the association of piloerection and epileptic seizures and recently recognized important relationship with autoimmunity as a newly described potential etiology. Furthermore at the end of the review we will discuss the etiology, localizing and lateralizing features of our illustrative case examples with pilomotor seizures. We would like also to draw attention to sudden unexplained death in epilepsy in one of our cases with pilomotor aura who had drug-resistant epilepsy associated with hippocampal sclerosis.

Keywords: Piloerection, goosebumps, temporal lobe epilepsy, limbic encephalitis, autoimmune epilepsy

INTRODUCTION
Piloerection or gooseflesh is a well-known defense reaction against danger in many species, represented best by porcupines which raise their quills when threatened. Its function in human ancestors might be related to raise the body's hair, making the ancestors appearance larger and scaring off predators. On the other hand, in humans piloerection is also evoked as a response to cold which is considered as remnant behavior of the thermoregulatory response of our furred ancestors in evolution.
review will discuss the association of piloerection and epileptic seizures and its etiological spectrum with emphasis on the newly discovered relationship with autoimmunity.

**Etiology of pilomotor seizures**

Pilomotor seizures are unusual autonomic seizures which have usually been reported with temporal lobe epilepsy (TLE).\(^{2,7,12,15,21,25}\) Their prevalence was estimated as 1.2% in a group of patients with TLE.\(^{21}\) There was no specific etiology associated with pilomotor seizures which were described in a wide variety of lesional epilepsies such as mesial temporal sclerosis (MTS), brain tumors, posttraumatic gliosis, cavernous malformations, limbic encephalitis and nonlesional (cryptogenic) epilepsy.\(^{6,7,12,13,14,15,16,17,19,21,24,25,26}\) Interestingly, recent reports demonstrated a new association of ictal piloerection with some forms of seropositive limbic encephalitis. The associated neuronal auto-antibodies were reported as LGI1, Hu, Ma2 and VGKC-complex antibodies, so far.\(^{14,15,24}\) In this series of patients, piloerection took place at a high daily frequency remarkably. Thus physicians encountering patients with pilomotor seizures should urgently initiate a search for related neuronal auto-antibodies and possibility of cancer in suspected cases.

**Localizing and lateralizing features of pilomotor seizures**

Seizures characterized by piloerection may occur unilaterally or bilaterally in the whole or some parts of the body-halfes. It usually accompanies other ictal behaviors like feelings of fear, experiential sensations, other types of autonomic aura, loss of awareness and automatisms.\(^{6,7,12,13,14,15,16,17,19,21,24,25,26}\)

Piloerection may be neglected if there are other prominent succeeding ictal behaviors and loss of consciousness.\(^{12}\) Furthermore video recordings may not be sensitive enough to catch ictal piloerection in video EEG monitoring (VEM) units, if not specifically reported by the patients or accompanying persons. Therefore the exact frequency of pilomotor events may be expected to be higher than recorded. Rarely piloerection may also be the sole seizure manifestation, called as pilomotor aura in the ILAE proposal.\(^{5}\)

The localizing and lateralizing value of ictal piloerection is uncertain. Previous case studies reported patients with ictal piloerection who had an ictal onset lateralized to the left hemisphere.\(^{21}\) However its lateralizing significance has been challenged.\(^{7,12,13,15}\) Loddenkemper et al. described a series of patients with unilateral piloerection which has been associated with ipsilateral seizure onset\(^{12}\) although some other reported patient series had contralateral skin involvement.\(^{16,15,21}\) Ipsilateral involvement of piloerection was also supported by other cases which suggested evidence of descending sympathetic fibers that are probably uncrossed.\(^{1,19,25,26}\) Furthermore ipsilateral piloerection was observed after electrical stimulation of posterior hypothalamic region.\(^{22}\) Our experience summarized in Table 1 may also suggest that if piloerection occurred unilaterally it mainly indicated an ipsilateral focus, whereas bilateral piloerection did not have any clear lateralizing value.

**Electrophysiological data**

The exact location of the generator of piloerection remains still unknown. Pilomotor seizures have been mainly associated with a temporal focus which suggests a functional relationship between limbic circuits, autonomic responses and an associated cutaneous reaction of the parietal lobe.\(^{15}\) However other structures outside the temporal lobe which are related to central autonomic network can also be responsible for piloerection.\(^{6,7,13,19}\) Loddenkemper et al. reported a patient with left temporal malformation of cortical development who had an ipsilateral pilomotor response after direct cortical stimulation of left parahippocampal
Moreover Mittal et al. reported a patient with a history of bilateral goosebumps associated with a right mesiotemporal tumor. Intracranial EEG findings during pilomotor seizures confirmed an epileptogenic focus in right temporal neocortex which primarily involved middle and superior temporal gyrus. Furthermore Seo et al. reported a case with pilomotor seizures which originate in right anterior cingulate gyrus which was confirmed by presurgical evaluation with ictal SPECT and electrocorticography. Following resection of the focus, the patient became seizure free. However in these particular cases not the epileptic focus, but rather the spreading after discharges within regions of autonomic control (posterior hypothalamus, anterior insula, orbitofrontal cortex, or anterior cingulate) might have induced these peculiar ictal phenomenon.

Central autonomic network and stimulation studies

Piloerection has been elicited by electrical or pharmacological stimulation in humans and animals at multiple sites including hippocampus, amygdala, hypothalamus, midbrain reticular core, and medial prefrontal cortices. These data support that the generator for ictal piloerection is located within or close to the central autonomic network which is a large system of neurons extending from forebrain to brainstem and includes insular and medial prefrontal cortices, the central nucleus of the amygdala, the preoptic region, the hypothalamus, the midbrain periaqueductal grey matter, the pontine parabrachial region, the nucleus of the solitary tract, and the intermediate reticular zone of the medulla. Further intracranial studies are needed in cases with pilomotor seizure events to elucidate these interesting networks and their interactions to give insight for normal physiology besides the epileptogenic pathways gaining importance in TLE.

Illustrative case reports:

In the following section we would like to present our case series with pilomotor aura. We reviewed our database for the patients who reported piloerection during seizures in their history. Of the 230 patients with drug resistant epilepsy who underwent VEM investigations, 5 patients (2.1%) with piloerection as the major seizure semiology were identified retrospectively. The clinical, neuro-imaging and EEG findings of these five patients with ictal piloerection were summarized in Table 1. The mean age at seizure onset was 13.8 years (range 1-30) and the average epilepsy duration was 19.6 years (range 7-33). All patients were diagnosed with TLE (3 left-sided and 2 right-sided). Magnetic resonance imaging (MRI) revealed hippocampal sclerosis in 4 and low grade parahippocampal tumor in one patient (Figure 1). Three patients were additionally examined with fludeoxyglucose-positron emission tomography (FDG-PET) which showed hypometabolism of the temporal lobe, concordant with the MRI findings. It is remarkable that all the patients had drug-resistant epilepsy.

Two patients underwent successful epilepsy surgery as seen in Table 1 (one left and the other one right-sided operations) and they became seizure-free for at least 12 months of follow-up. Unfortunately, another one patient diagnosed with right mesial TLE associated with hippocampal sclerosis (patient 4) who had completed the preoperative diagnostic investigations and was on the surgery list had died due to possible sudden unexpected death in epilepsy (SUDEP) at the age of 37 years. He did not have any known health problems and seemed as an ordinary patient with right-sided TLE except the rare association with pilomotor seizures.
Table 1: The Clinical and Laboratory Features of Patients with Pilomotor Aura

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)/sex/Handedness</td>
<td>34/M/R</td>
<td>36/M/R</td>
<td>29/F/R</td>
<td>37/M/R</td>
<td>31/M/L</td>
</tr>
<tr>
<td>Epilepsy duration (years)</td>
<td>33</td>
<td>23</td>
<td>18</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Epilepsy syndrome Etiology</td>
<td>L TLE MTLE-HS</td>
<td>L TLE MTLE-HS</td>
<td>R TLE MTLE-HS</td>
<td>R TLE MTLE-HS</td>
<td>L TLE MTLE-HS</td>
</tr>
<tr>
<td>Personal history</td>
<td>Meningitis, febrile seizures</td>
<td>NS</td>
<td>Tbc meningitis, febrile seizures</td>
<td>NS</td>
<td>Meningitis, polycystic kidney disease, renal transplantation</td>
</tr>
<tr>
<td>Family history</td>
<td>NS</td>
<td>NS</td>
<td>Consanguineous marriage</td>
<td>NS</td>
<td>Consanguineous marriage</td>
</tr>
<tr>
<td>Psychiatric features</td>
<td>Depression</td>
<td>NS</td>
<td>Depression, psychotic spells, postoperative hypersexuality</td>
<td>NS</td>
<td>Pseudoseizures</td>
</tr>
<tr>
<td>Seizure types Type of aura</td>
<td>Focal, SGS Epigastric, pilomotor</td>
<td>Focal, SGS Affective, pilomotor</td>
<td>Focal, SGS, Focal SE Affective, pilomotor</td>
<td>Focal, SGS Palpitation, gustatory, pilomotor</td>
<td>Focal Pilomotor, hyperacusia</td>
</tr>
<tr>
<td>Piloerection</td>
<td>Bilateral</td>
<td>Left arm</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>Back</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>3-4/month L HS</td>
<td>3-4/month L HS</td>
<td>5-7/month R HS</td>
<td>3-4/month R HS</td>
<td>1-2/month L para-hippocampal low grade tumor</td>
</tr>
<tr>
<td>MRI findings</td>
<td>L HS</td>
<td>L HS</td>
<td>R HS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PET findings</td>
<td>Bilateral temporal hypometabolism</td>
<td>L temporal hypometabolism</td>
<td>R inferior temporal hypometabolism</td>
<td>-</td>
<td>L F sharp waves</td>
</tr>
<tr>
<td>Interictal EEG findings</td>
<td>L FT sharp waves, L TIRDA</td>
<td>L FT, FP sharp waves, L FT theta</td>
<td>R FT spikes and slow waves</td>
<td>R FT spikes, R TIRDA</td>
<td>3 sz from L hemisphere (Figure 2)</td>
</tr>
<tr>
<td>Ictal EEG findings</td>
<td>2 sz from L FT area, 1 NL sz</td>
<td>2 sz from L FT, 1 NL sz</td>
<td>6 subclinical sz from R FT area</td>
<td>6 sz from R FT area</td>
<td>Hypersalivation</td>
</tr>
<tr>
<td>Other autonomic findings</td>
<td>Tachycardia, genital automatism</td>
<td>-</td>
<td>-</td>
<td>Tachycardia, genital automatism</td>
<td>-</td>
</tr>
<tr>
<td>AED treatment</td>
<td>CBZ 800 mg, LTG 400 mg</td>
<td>CBZ 1000 mg, LTG 400 mg, TOP 150 mg</td>
<td>OXC 1200 mg, LTG 100 mg, TOP 200 mg</td>
<td>LTG 400 mg, TOP 100 mg</td>
<td>LEV 2500 mg, CBZ 1000 mg</td>
</tr>
<tr>
<td>AED response Treatment and prognosis</td>
<td>Poor Engel 2 for 1 years after L temporal lobectomy</td>
<td>Poor On the surgery list (he denied the operation)</td>
<td>Poor Engel 1 for 8 years after R amygdalo-hippocampectomy</td>
<td>Poor Exitus (SUDEP)</td>
<td>Poor On the surgery list (operation was postponed due to renal problems)</td>
</tr>
</tbody>
</table>

Three patients experienced bilateral piloerection, one of them had initially unilateral piloerection on the left arm which was followed by a testicular retraction feeling and another one had piloerection on the back. Piloerection was preceded or associated by feeling of ictal cold, epigastric aura, gustatory aura, fear, depression and palpitations. Other associated ictal autonomic features were tachycardia, genital automatisms and hypersalivation.

Case example associated with anti-neuronal antibody

A 38-year-old right-handed woman (patient 3 in the Table 1) had reported episodes starting at the age of 11 years which manifested as fear and feeling of abuse from other people. She experienced goosebumps in all parts of her body which was followed by sudden forced thinking of a mouse. In the following years she suffered from other episodes which

**Figure 1:** MRI images showing a hyperintense lesion involving subcortical area in left parahippocampal gyrus. MRI images and proton MR spectroscopy findings are consistent with a low grade glial tumor (patient 5).

**Figure 2:** Video EEG monitoring shows left fronto-temporal 3-4 Hz semi-rhythmic slow waves at the beginning of a seizure correlating with the onset of piloerection on the patients' back (patient 5).
occurred 2-3 times per week and associated with loss of consciousness, right version, automatisms in the right hand and rare secondarily generalized seizures. Her mother noticed a nasty odor in her body when she had a seizure. She had history of focal status epilepticus after inappropriate drug withdrawal. She usually experienced an increase in seizure frequency around the time of menstruation. At the age of 14 years, she was also presented with interictal psychotic symptoms, depression and obsessive compulsive disorder. She was hospitalized twice in a psychiatric hospital. Despite various antiepileptic drug polytherapies her seizures persisted.

She had history of tuberculous meningitis and prolonged febrile seizures when she was 1.5 years. Her parents had consanguineous marriage and her father had lung tuberculosis. The brain MRI showed a right temporal hippocampal sclerosis. PET scan revealed hypometabolism in the right inferior temporal lobe. Ictal EEGs demonstrated a right frontotemporal seizure onset. She underwent right selective amygdalo-hippocampectomy and histology revealed diffuse cell loss which was congruent with the diagnosis of mesial temporal sclerosis. She is seizure free for 8 years. However her psychiatric symptoms persisted after surgery with increasing hyper-religious behaviors and hypersexual thoughts with incest content. Due to atypical seizure semiology which was reported with antineuronal antibodies and history of psychotic episodes she underwent a comprehensive evaluation of autoimmune and paraneoplastic markers. Serum analysis showed anti- GABA-A receptor antibodies, which were found for the first time in association with TLE and psychosis besides with pilomotor seizures.

Our patient series further demonstrates that ictal piloerection is a rare but consistent feature of TLE which is concordant with most of the previously reported case series.\(^{(2,12,15,21)}\) The prevalence of ictal piloerection among patients with chronic epilepsy was found 2.1 % which is again in the same range as reported previously.\(^{(4)}\) Three of our patients had left and two of them had right-sided TLE which corroborates no lateralizing value for ictal piloerection. Most of the patients in our series had bilateral or whole body skin involvement except one who had unilateral onset of piloerection and ipsilateral seizure onset. Our unique case with GABA-A receptor antibody positivity may suggest an association of piloerection with GABA-ergic autoimmunity and prompt a search for these antibodies in patients with pilomotor aura.

**CONCLUSION**

Piloerection seizures are seen uncommonly and may result from diverse brain pathologies, besides the possible association with autoimmunity which may prompt a search for paraneoplastic and nonparaneoplastic neuronal auto-antibodies. The lateralizing and localizing value of piloerection is unclear, although left temporal seizures are frequently seen. Unilateral piloerection may associate with ipsilateral seizure onset. Onset of seizure in central autonomic network or spread of ictal discharges may generate pilomotor seizures. It is worth to emphasize that pilomotor aura was seen in one of our patients who deceased due to SUDEP. Although this unfortunate event could be a chance association based on the underlying drug-resistant epilepsy, the existence of pilomotor seizures related to unknown interactions of central autonomic pathways may indicate autonomic instability and may warrant cardiac autonomic studies in suspected patients.

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REFERENCES


